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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,877	06/23/2000	Johan Lennerstrand	07691.0004	1424

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	17

DATE MAILED: 03/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,877	LENNERSTRAND ET AL.	
	Examin r	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 20, and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Office Action

37 C.F.R. § 1.114

1. A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114.

Status of the Claims

2. Acknowledgement is hereby made of receipt and entry of the amendment submitted 21 February, 2003, wherein claims 1, 14, 20, and 21 were amended. Claims 15-19 stand withdrawn from further consideration by the examiner, pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Claims 1-14, 20, and 21 are currently under examination.

35 U.S.C. § 112, Second Paragraph

3. Claims 1-14, 20, and 21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. The claims (1, 20, and 21) have been amended to include the phrase "entities that result from the interaction of substances" which is completely vague and indefinite. The skilled artisan cannot readily ascertain the meaning of this phrase. The claims have also been amended to include an additional limitation that recites an "enzymatic kinetics assay" without providing any of the details of said assays. The claims are deficient since they fail

to provide any of the required experimental parameters. Applicants are directed toward pp. 23 and 24 of the disclosure for suggestions in drafting appropriate claim language.

5. Claims 13 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims reference various mutations at specific amino acid locations. However, it is not readily manifest if the mutations reference HIV-1 or -2. The specification describes mutations that are present in the HIV-1 RT, not HIV-2. Moreover, HIV-1 and -2 display considerable genotypic and phenotypic heterogeneity, thus it is not readily manifest that the same mutations associated with HIV-1 resistance correspond to the same locations in HIV-2. Appropriate correction is required.

6. Claim 14 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment to the claim still fails to overcome the deficiency present. The claim still references insertional mutations at codon 69. It is not readily manifest how a single amino acid could contain an insertion. It is either substituted or deleted. If additional amino acids are inserted between this amino acid and another amino acid (i.e., aa 70), this should be clearly set forth in the claim language (i.e., wherein there is an insertional mutation between aa 69 and 70). Appropriate amendment to the claim language is required.

35 U.S.C. § 112, First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the

> invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-14, 20, and 21 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The claims have been amended to include the limitation "performing an enzymatic kinetics assay that permits the measurement of multiple chain termination events by adding to the reaction well ...". Support does not exist for this particular limitation in the specification.

The disclosure purportedly describes a "novel" reverse transcriptase (RT) assay. What the disclosure describes is a generic RT assay comprising the following:

> ... the method provides a reaction well comprising a template for an HIV RT enzyme, a primer, a detectable dNTP substrate, an HIV RT inhibitor, and a ribonucleotide chosen from ATP and GTP or a pyrophosphate. An HIV RT enzyme is then added to the reaction well, wherein the HIV RT enzyme incorporates the detectable dNTP substrate of the HIV RT inhibitor into the template. The HIV RT enzyme may be chosen from a wild-type RT enzyme or a mutant RT enzyme. The RT activity is then determined by measuring the amount of the detectable dNTP substrate that is incorporated into the template, and the resistance of HIV to the HIV RT inhibitor is determined from the RT activity.

Additional experimental details are provided on pages 23 and 24 of the disclosure. However, nothing contained therein supports the limitation introduced directing the invention towards the measurement of multiple chain termination events. Appropriate

correction is required.

35 U.S.C. § 103(a)

9. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103© and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

11. The factual inquiries set forth in *Graham et al. v. John Deere Company of Kansas City et al.; Calmar, Inc. v. Cook Chemical Company; Colgate-Palmolive Company v. Same*, 148 U.S.P.Q. 459 (U.S. Sup. Ct. 1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows: 1) Determining the scope and contents of the prior art. 2) Ascertaining

the differences between the prior art and the claims at issue. 3) Resolving the level of ordinary skill in the pertinent art. 4) Considering objective evidence present in the application indicating obviousness or unobviousness.

12. Claims 1-3, 5-12, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996). The claims are directed toward an HIV RT assay to assess the resistance of any given RT sample to treatment with an HIV RT inhibitor. The claims require a reaction well with the following components: (i) at least one template for an HIV RT enzyme; (ii) at least one primer; (iii) at least one detectable dNTP substrate; (iv) at least one HIV RT inhibitor; and (v) at least one ribonucleotide chosen from ATP and GTP, or at least one pyrophosphate. Additional steps recite comparative steps involving both the wildtype and mutant RTs.

As previously set forth, Meyer *et al.* (1999) provide an HIV RT enzymatic assay to examine mutant activity that employs at least one template, at least one primer, at least one RT inhibitor, and either ATP/GTP or pyrophosphate (see Experimental Procedures, p. 42). The authors reported (p. 35, rt. col.) that "we describe an in vitro assay that reproduces the essential in vivo properties of the AZT resistance mutants. HIV-1 RT containing the D67N, K70R, T215F, and K219Q amino acid substitutions (designated as 67/70/215/219 RT in this report) was much more efficient than WT RT at extending the primer past several potential termination sites in the presence of AZTTP when ATP was added to the reaction. Transfer of the AZTMP residue from the primer terminus to ATP to form dinucleoside polyphosphate and unblocked primer was enhanced in the 67/70/215/219 RT."

The authors also noted (see p. 35, last paragraph, rt. col.) that the "Addition of a ribonucleoside triphosphate (ATP) to the reaction mixture provided an acceptor for the nucleotide-dependent

primer unblocking activity in which the AZTMP residue from the chain-terminated primer was transferred to ATP to form Ap_4AZT, and the primer was shortened by one residue and was no longer blocked to elongation". The authors finally conclude (see p. 36, rt. col.) that "by adding ATP at concentrations likely to be present in intact cells, we have established an in vitro system that reflects the in vivo properties of the 67/70/215/219 mutant virus." This teaching does not disclose an RT assay that employs a detectable dNTP.

However, as previously set forth, Ekstrand *et al.* (1996) provide a non-radioactive reverse transcriptase assay that employs 5-bromodeoxyuridine 5'-triphosphate (BrdUTP) as the detectable dNTP (see Materials and Methods, p. 97). The assay described employs an alkaline phosphatase-conjugated anti-BrdU antibody and provides quantitative results. The authors note (see p. 104, last paragraph) "the present paper describes a simple, sensitive and non-radioactive RT assay with kinetic features similar to those observed when the natural dTTP substrate is used."

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Meyer *et al.* (1999), since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription.

13. Applicants again contend that sufficient motivation and a reasonable expectation of success were not present in the prior art. These arguments are clearly not persuasive in view of the prior art. Moreover, as previously set forth, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary

references. *In re Nomiya*, 184 U.S.P.Q. 607 (C.C.P.A. 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 U.S.P.Q. 209 (C.C.P.A. 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 U.S.P.Q. 545 (C.C.P.A. 1969). As set forth *supra*, both the motivation and a reasonable expectation of success were present in the prior art. One of ordinary skill in the art would have had sufficient motivation to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Meyer *et al.* (1999), since this would provide a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription.

14. Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ueno *et al.* (1995). The content of Meyer *et al.* (1999) is disclosed in the preceding paragraph. Meyer and colleagues do not describe the utilization of an art-recognized RT activity label such as a radioactive dNTP, although a labeled primer was employed. However, Ueno *et al.* (1995) describe standard HIV RT assays that employ art-recognized labels such as radioactive labeled dNTPs (see pp. 23605-23606, EXPERIMENTAL PROCEDURES, *Materials* and *Product Analysis*). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize a radiolabeled dNTP, as taught by Ueno *et al.* (1995), in the assay of Meyer *et al.* (1999), since this represents a standard and art-recognized means for detecting RT reaction products. Applicants' arguments are not convincing as noted in the preceding paragraph.

15. Claims 13 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996), as applied *supra* to claims 1-3, 5-12, 20, and 21, and further in view of Larder *et al.* (1999a, 1999b). The combination of references employed *supra* do not disclose the use of HIV RT mutants carrying mutations at amino acid positions 67, 69, and 70, or an insertion between amino acids 69 and 70. However, both Larder *et al.* (1999a, 1999b) publications disclose that HIV-1 RT resistant variants, particularly MNR variants, carry mutations at amino acids 67, 69, and 70, and between amino acids 69 and 70. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the HIV-1 RT mutants described by Larder *et al.* (1999a, 1999b), in the reverse transcriptase assay suggested by Ekstrand *et al.* (1996) and Meyer *et al.* (1999). One of ordinary skill in the art would have been motivated to include these mutant forms of the RT since they naturally develop during the course of antiviral therapy. Applicants' arguments are not convincing for the reasons of record set forth *supra*.

16. Claims 1-3, 5-12, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ekstrand *et al.* (1996). Arion *et al.* (1999) provides an HIV RT enzymatic assay to examine mutant activity that employs a template, primer, RT inhibitor, and pyrophosphate (see p. 15910, MATERIALS AND METHODS, *Analysis of Chain Termination of RT-Catalyzed DNA Synthesis*). The authors suggested (see p. 15908, ABSTRACT) that "HIV-1 resistance to AZT results from the selectively decreased binding of AZTTP and the increased pyrophosphorolytic cleavage of chain-terminated viral DNA by the mutant RT at physiological pyrophosphate levels, resulting in a net decrease in chain termination. The increased processivity of viral DNA synthesis may

be important to enable facile HIV replication in the presence of AZT, by compensating for the increased reverse reaction rate." This teaching does not disclose an RT assay that employs a detectable dNTP.

However, Ekstrand *et al.* (1996) provide a non-radioactive reverse transcriptase assay that employs 5-bromodeoxyuridine 5'-triphosphate (BrdUTP) as the detectable dNTP (see Materials and Methods, p. 97). The assay described employs an alkaline phosphatase-conjugated anti-BrdU antibody and provides quantitative results. The authors note (see p. 104, last paragraph) "the present paper describes a simple, sensitive and non-radioactive RT assay with kinetic features similar to those observed when the natural dTTP substrate is used."

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Arion *et al.* (1998), since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription.

17. Applicants again argue that both sufficient motivation and a reasonable expectation of success were not present in the prior art is not convincing. These arguments are clearly not persuasive in view of the prior art and knowledge of the skilled artisan. Moreover, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. *In re Nomiya*, 184 U.S.P.Q. 607 (C.C.P.A. 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of

ordinary skill in the art. *In re McLaughlin*, 170 U.S.P.Q. 209 (C.C.P.A. 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 U.S.P.Q. 545 (C.C.P.A. 1969). As set forth supra, both the motivation and a reasonable expectation of success were present in the prior art. One of ordinary skill in the art would have had sufficient motivation to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Arion *et al.* (1998), since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription.

18. Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ueno *et al.* (1995). The content of Arion *et al.* (1998) is disclosed in the preceding paragraph. Meyer and colleagues do not describe the utilization of an art-recognized RT activity label such as a radioactive dNTP, although a labeled primer was employed. However, Ueno *et al.* (1995) describe standard HIV RT assays that employ art-recognized labels such as radioactive labeled dNTPs (see pp. 23605-23606, EXPERIMENTAL PROCEDURES, *Materials* and *Product Analysis*). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize a radiolabeled dNTP, as taught by Ueno *et al.* (1995), in the assay of Arion *et al.* (1998), since this represents a standard and art-recognized means for detecting RT reaction products. Applicants' arguments are not convincing for the reasons set forth in the preceding paragraph.

19. Claims 13 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ekstrand *et al.* (1996), as applied *supra* to claims 1-3, 5-12, 20, and 21, and

further in view of Larder *et al.* (1999a, 1999b). The combination of references employed *supra* do not disclose the use of HIV RT mutants carrying mutations at amino acid positions 67, 69, and 70, or an insertion between amino acids 69 and 70. However, both Larder *et al.* (1999a, 1999b) publications disclose that HIV-1 RT resistant variants, particularly MNR variants, carry mutations at amino acids 67, 69, and 70, and between amino acids 69 and 70. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the HIV-1 RT mutants described by Larder *et al.* (1999a, 1999b), in the reverse transcriptase assay suggested by Ekstrand *et al.* (1996) and Arion *et al.* (1998). One of ordinary skill in the art would have been motivated to include these mutant forms of the RT since they naturally develop during the course of antiviral therapy. Applicants' arguments are not convincing for the reasons of record set forth *supra* in paragraph 9.

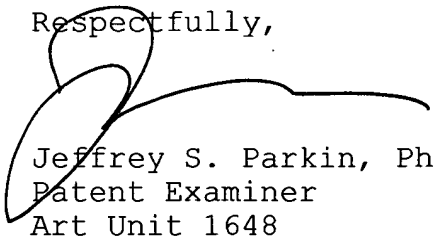
Correspondence

20. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

21. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122,

respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,



Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

23 March, 2003